

Listing of the Claims:

This listing of claims will replace all prior versions and listings of claims in the application.

1. (original) A medical agent comprising an anti-CD20 antibody or variants thereof conjugated to 1.5 to 3.5 reagents, wherein each reagent comprises

a) a trifunctional cross-linking moiety selected from the group consisting of triaminobenzene, tricarboxybenzene, dicarboxyaniline and diaminobenzoic acid, coupled to

b) a biotin molecule selected from the group consisting of biotin and biotin derivatives having essentially the same binding function to avidin or streptavidin as biotin, via a linker 1, wherein the linker 1 contains hydrogen bonding atoms, preferably ethers or thioethers, or ionisable groups, preferably carboxylate, sulphonates and ammonium to aid in water solubilisation of the biotin moiety, and stability against enzymatic cleavage has been provided by introducing substituents to the biotinamide amine or to an atom adjacent to that amine, to

c) an effector agent covalently linked to the trifunctional cross-linking moiety, optionally via a linker 2, wherein the linker 2 provides a spacer length of 1-25 atoms and the linker contains hydrogen bonding atoms, preferably ethers or thioethers, or ionisable groups to aid in water solubility, and to

d) a linker 3, which covalently links the anti-CD20 antibody to the reagent, wherein the linker 3 provides a spacer length of 1-25 atoms and contains hydrogen bonding atoms, preferably ethers or thioethers, or ionisable groups to aid in water solubility, wherein the anti-CD20 antibody is selected from a group of antibodies or variants thereof having a specific binding to CD20 antigens and having an affinity binding constant of at least $5 \times 10^6 \text{ M}^{-1}$.

2. (original) The medical agent according to claim 1, wherein the anti-CD20 antibody is conjugated with from 3 to 4 reagents.

3. (previously presented) The medical agent according to claim 1, wherein the

affinity binding constant is at least 10^8 M^{-1} .

4. (previously presented) The medical agent according to claim 1, wherein the anti-CD20 antibody is ibritumomab, rituximab, or tositumomab.

5. (original) The medical agent according to claim 4, wherein the anti-CD20 antibody is rituximab.

6. (previously presented) The medical agent according to claim 1, wherein the linkers 2 and 3 provide a spacer length of 6-18 atoms.

7. (previously presented) The medical agent according to claim 1, wherein the anti-CD20 antibody variant has the same or essentially the same ability as the anti-CD20 antibody to bind to both the anti-CD20 antibody reacting moiety and said CD antigen/antigens on the surface of a lymphoma tumour cells, and wherein said variant is an antibody derivative, preferably the F(ab')₂, F(ab') or F(ab) fragment, genetically engineered hybrids or chemically synthesized peptides, preferably chimeric or humanized antibodies, and single chain antibodies.

8. (previously presented) The medical agent according to claim 1, wherein the effector agent is a radio-nuclide binding moiety, optionally provided with a radionuclide, a synthetic or naturally occurring toxin, an enzyme capable of converting pro-drugs, immunosuppressive or immunostimulating agents, radiosensitizers, enhancers for X-ray of MRI or ultrasound, non-radioactive elements, which can be converted to radioactive elements by means of external irradiation after the anti-CD20 antibody carrying said element has been accumulated to specific cells or tissues, or photoactive compounds or compounds used in photo-imaging or photodynamic therapy, or any other molecule having the same or similar effect, directly or indirectly, on lymphoma cells or lymphoma tissues.

9. (original) The medical agent according to claim 8, wherein the effector agent is

provided with positron-imaging radionuclides, preferably F-18, Br-75, Br-76 and I-124; therapeutic radionuclides, preferably Y-90, I-131, In-114m, Re-186, Re-188, Cu-67, Sm-157, Lu-177, Bi-212, Bi-213, At-211, Ra-223, gamma-imaging radionuclides, preferably Tc-99m, In-111, I-123 and I-125, beta-radiation emitters, preferably scandium-46, scandium-47, scandium-48, copper-67, gallium-72, gallium-73 yttrium-90, ruthenium-97 palladium-100, rhodium-101, palladium 109, samarium-153, lutetium-177, rhenium-186, rhenium-188, rhenium-189, gold-198, radium-212, and lead-212, gamma emitters, preferably iodine-131 and indium-114 and positron emitters, preferably gallium-68 and zirconium-89.

10. (original) The medical agent according to claim 9, wherein the effector agent comprises aryl halides and vinyl halides for radionuclides of halogens, N_2S_2 and N_3S chelates for Tc and Re radionuclides, amino-carboxy derivatives, preferably EDTA and DTPA or derivatives thereof, and cyclic amines, preferably NOTA, DOTA and TETA, and derivatives thereof, for In, Y, Pb, Bi, Cu, Sm and Lu radionuclides, or any other radionuclide capable of forming a complex with said chelates.

11. (original) The medical agent according to claim 10, wherein the effector agent comprises DOTA and is provided with Y-90 or Lu-177 for therapeutic application or In-111 for diagnostic purposes.

12. (previously presented) The medical agent according to claim 1, wherein the biotin derivative is selected from the group consisting of norbiotin, homobiotin, oxybiotin, iminobiotin, destibiotin, diaminobiotin, biotin sulfoxide, and biotin sulfone, or derivatives, preferably norbiotin or homobiotin.

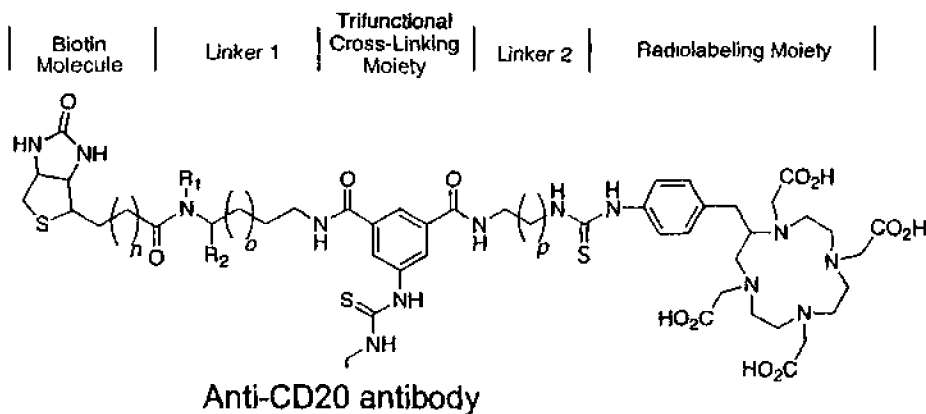
13. (previously presented) The medical agent according to claim 1, wherein the biotinamide amine substituents are $-CH_2OH$ or $-CO_2H$ and the substituents adjacent to the biotin amine are $-CH_3$ or $-CH_2OH$.

14. (previously presented) The medical agent according to claim 1 wherein the anti-

CD20 antibody has been covalently bound to the reagent, optionally via the linker 3, through a reaction of a group of active esters consisting of N-hydroxysuccinimide esters, sulfo-N-hydroxysuccinimide esters, and phenolic esters; aryl and alkyl imidates; alkyl or aryl isocyanates or isothiocyanates, with amino groups on the anti-CD20 antibody; or a reaction of maleimides or alpha-haloamides with sulfhydryl groups on the anti-CD20 antibody; or a reaction of aryl or alkylhydrazines or alkyl or arylhydroxylamines with aldehyde or ketone groups naturally occurring or synthetically produced on the anti-CD20 antibody.

15. (previously presented) The medical agent according to claim 1, wherein the linker 2 is excluded.

16. (previously presented) The medical agent according to claim 1, wherein it is



wherein the anti-CD20 antibody preferably is rituximab, wherein n is 2-4, preferably 3, o is 1-6, preferably 3, p is 1-6, preferably 3; R₂ is -CH₂OH or -CO₂H; and R₁ is -CH₃, -CH₂OH or -H.

17. (original) The medical agent according to claim 16, wherein it is 3-(13'-thiourea benzyl-(DOTA)trioxadiazine-1-(13"-biotin-Asp-OH)trioxadiazine-5-isothiocyanato-aminoisophthalate-ibritumumab, 3-(13'-thiourea benzyl-(DOTA)trioxadiazine-1-

(13"-biotin-Asp-OH)trioxamine-5-isothio-cyanatoaminoisophtalate-rituximab, or 1-Isocyanato-3-((1 S'-(N-Biotinyl)-(β-L-Aspartyl)-4',7',10'-Trioxa-penta-Decanyl-amino)-1-((13-(Benzylthiourea-CHX-A")-4,7,10-Trioxatridecanediamine)-Aminosio-phthalate-rituximab, preferably 3-(13'-thiourea-benzyl-(DOTA)trioxadamine-1-(13"-biotin-Asp-OH)trioxamine-5-isothio-cyanato-aminoisophtalate-rituximab.

18. (previously presented) The medical agent according to claim 1, wherein it further comprises physiologically acceptable additives, preferably an ammonium acetate solution.

19. (previously presented) A medical agent according to claim 1, with the proviso that said reagent/reagents is/are covalently bound to the anti-CD20 antibody without the linker 3.

20. (withdrawn) A kit for extracorporeal elimination or at least reduction of the concentration of a non-tissue bound therapeutic or diagnostic medical agent as defined in claim 1 in the plasma or whole blood of a mammalian host, wherein said medical agent previously has been introduced into a mammalian host and kept therein for a certain time in order to be concentrated to the specific tissue or cells by being attached thereto, said kit comprising:

- a) the medical agent, and
- b) an extracorporeal device comprising an immobilised receptor to which a biotin molecule adheres.

21. (withdrawn) A method for treating lymphoma, comprising administering an effective amount of the medical agent according to claim 1 to a patient in need thereof.

22. (previously presented) A medicament for the treatment of lymphoma comprising the medical agent according to claim 1.

23. (withdrawn) A method for treatment of lymphoma, comprising:
administering anti-lymphoma antibodies or variants thereof to a patient in need of treatment, wherein complexes formed between said anti-lymphoma antibodies or variants thereof and leukocytes having one or more cell surface antigen(s) are then eliminated from the body of the patient, followed by
administering the medical agent according to claim 1, optionally together with said anti-lymphoma antibodies or variants thereof as such, followed by
extracorporeal elimination of the medical agent which has not been bound to the cell surface antigens on the lymphoma tumour cells.
24. (withdrawn) The method according to claim 23, wherein the effector agent of the medical agent is ^{90}Y and the medical agent is administered in a single dose of more than 20 MBq/kg body weight.
25. (withdrawn) A method for diagnosing lymphoma comprising
administering anti-lymphoma antibodies or variants thereof to a patient in need thereof, wherein complexes formed between said anti-lymphoma antibodies or variants thereof and leukocytes having one or more cell surface antigen(s) are then eliminated from the body of the patient, followed by
administering the medical agent according to claim 1, optionally together with said anti-lymphoma antibodies or variants thereof as such, followed by
extracorporeal elimination of the medical agent which has not been bound to the cell surface antigens on the lymphoma tumour cells.
26. (withdrawn) The method according to claim 25, wherein the effector agent of the medical agent is ^{90}Y or ^{111}In and the medical agent is administered in a dose range of 10-20, preferably 11-15, MBq/kg body weight in view of ^{90}Y and in a dose range of 20-250, preferably 50-150, MBq/kg body weight in view of ^{111}In .
27. (withdrawn) A method for combined diagnosing and treatment of lymphoma, comprising administering a first group of medical agent and a second group of medical

agent to a patient in need thereof either in sequence at intervals of 6-8 days or simultaneously,

wherein the medical agents of both groups are the medical agents according to claim 1, and

wherein in the medical agent of the first group, the effector agent is ^{111}In and is administered in a dose range of 50-150 MBq/kg body weight, and

in the medical agent of the second group the effector agent is ^{90}Y and is administered in a dose of more than 20 MBq/kg body weight.